Section of Medicine

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Dialysis [*Abridged*]

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Hæmodialysis in the Treatment of Acute Poisoning

Hæmodialysis was first used in 1913 for the removal of salicylic acid in experimental poisoning (Abel *et al.* 1914) but was not tried clinically until 1950 when it was used for the treatment of aspirin poisoning (Doolan *et al.* 1951). Since then it has been used on a considerable scale. There are many published reports on its apparent great value in the treatment of exogenous poisoning (Schreiner 1958, Schreiner & Maher 1960, Jørgensen & Wieth 1963, Hagstam & Lindholm 1964) as well as a vast unpublished experience. Provided the poison in question satisfies certain requirements concerning dialysability, which I will consider later, the patient has been dialysed. An approximate list of the poisons which have been submitted to dialysis is shown in Table 1. In many cases the patient is said to improve or to be resuscitated though hardly any 'poison' has been removed in the dialysate. Here it is worth while remembering that more than 30% of patients take more than one poison and also that ethyl alcohol is very easily and successfully dialysed. Unless the other poisons including alcohol are suspected and looked for, improvement by dialysis could be due to the removal of a poison not even considered; often it is said to be due to removal of the ubiquitous 'unidentified metabolite'. Alternatively failure of dialysis could be due to the presence of an undialysable and unsuspected poison.

Almost every model of kidney machine has been used for extracorporeal hæmodialysis in acute exogenous poisoning, the Twin-coil more than any other, but there are published data on the use of the Kolff rotating drum, Skeggs-Leonards hæmodialyser, the Standard Kiil, the 4-layer Kiil, the Alwall Kidney and, for children, mini-Twin-coil, single coil of Twin-coil, special mini-Kiil, and single layers of the standard Kiil.

Table 1
Poisons that can be dialysed

Alcohols: Primary – methyl; ethyl; tertiary – methylpentynol (Oblivon), ethchlorvynol (Arvynol)
Amanita phalloides
Amphetamines (Dextro-Amphetamine)
Aniline
Antibiotics: Ampicillin, cephaloridine, chloramphenicol, cycloserine, kanamycin, neomycin, nitrofurantoin, penicillin, polymyxin, streptomycin, sulphonamides, tetracycline, vancomycin
Arsenic
Barbiturates
Boric acid
Bromides
Carbon tetrachloride
Chloral hydrate
Chlorates
Chloride (sodium chloride poisoning in children)
Chromic acid
Citrates
Cyclophosphamide
Dichloroethane
Dichromate (potassium salt)
Dichlorphenazone (Welldorm)
DNOC
Ergotamine
Ethchlorvynol (Placidyl)
Ethinamate (Valmid)
Ethylene glycol
Eucalyptus oil
Fluorides
5-Fluorouracil
Gallamine triethiodide
Glutethimide (Doriden)
Isoniazid
Iodides
Iron (+ chelating agents)
Lead (+ chelating agents)
Lithium
Meprobamate
Mercury
Methaqualone (Melsedin and, with dephenhydramine, as Mandrax)
Methotrexate
Methyprylone (Noludar)
Monoamine-oxidase inhibitors: Pargyline (Eutonyl), phenelzine (Nardil), tranylcypromine (Parnate)
Orphenadrine (Disipal)
Paracetamol
Paraldehyde
Phenacetin
Phenformin
Phenytoin (Epanutin)
Primidone (Mysoline)
Salicylates (aspirin; methyl salicylate)
Strontium
Thiocyanate (potassium salt)

In hæmodialysis for poisoning it is necessary to maintain a high rate of flow and this may necessitate the use of a blood pump in circuit. The efficiency of dialysis as measured by the clearance rate of the poison and the half-life of the blood level, other things being equal, is related to the surface area of the dialysing membrane. Dialysis for poisoning has been continued for as long as 18 hours, and for some poisons such as glutethimide (Doriden) which is sequestrated in fat, or aspirin, methyl salicylate, barbiturates or alcohol where further gut absorption occurs, it may be necessary to repeat the dialysis. Varying dialysing fluids have been used or recommended on an experimental basis, e.g. containing plasma for paracetamol, albumin for barbiturates, fat emulsions for glutethimide or stabilized with THAM for salicylates and some barbiturates. Finally, extracorporeal hæmodialysis is not an exclusive procedure and other eliminating procedures can be carried out and may need to be carried out at the same time, e.g. forced diuresis for methyprylone (Noludar) poisoning, &c.; forced alkaline diuresis for salicylates and possibly some barbiturates; peritoneal dialysis and exchange transfusion.

Requirements for extracorporeal hæmodialyses have been stated, partly based on the properties of the poison and partly on clinical experience (Schreiner 1958, and others). These can be summarized as follows:

(1) The poison satisfies the criteria for a dialysable poison: (*a*) That it is diffusible at a reasonable rate through a dialysis membrane from plasma water. (*b*) That it is freely accessible to dialysis from body water. (*c*) That toxicity is reasonably related to the level of this accessible removable poison. If these requirements are satisfied, then extracorporeal hæmodialysis is worth considering if the following are applicable.
(2) That hæmodialysis makes an appreciable addition to the body's own mechanism for detoxifying the position: (*a*) That hæmodialysis is quicker than these natural mechanisms. (*b*) That the body's own detoxifying mechanisms are not functioning adequately (oliguria, anuria, congestive heart failure, pulmonary œdema, circulatory collapse).
(3) That the poison being considered has a high possibility of producing renal or other damage during its handling by the body (methyl alcohol, ethylene glycol and some related substances, mercuric chloride).
(4) That the patient's clinical condition is deteriorating during treatment without hæmodialysis.
(5) That the level of poison in the blood is so high when the patient is first seen that clinical experience suggests there is a high probability of a fatal outcome in that patient.

With these criteria in mind extracorporeal hæmodialysis could become the treatment of choice with some poisons. Table 2 indicates such a list – hedged in by numerous restrictions but where hæmodialysis must be seriously considered. In the so-called 'nephrotoxic' exogenous poisons (marked ● in Table 2) hæmodialysis needs to be seriously considered in these before onset of symptoms.

Table 2
Poisons where dialysis is possibly the treatment of choice (in the absence of overt renal damage)

Alcohols:
Methyl (blood level 50 mg/100 ml or higher) ●
Ethyl (blood level 300 mg/100 ml or higher)
Aniline (in early stages of poisoning)
Arsenic
Barbiturates:
Barbitone (blood level above 30 mg/100 ml)
Phenobarbitone (blood level above 20 mg/100 ml)
Carbon tetrachloride ●
(within 48 hours of exposure)
Chloral hydrate
Ethylene glycol ●
(within 48 hours of exposure –
single dose of 60 ml
or ingestion of 15 ml
for 5 days or more)
Fluoride (immediately patient is seen) ●
Glutethimide (blood level above 3 mg/100 ml)
Iron (+ chelating agent – serum iron
levels above 750 µg/100 ml)
Lead (+ chelating agent)
Mercuric chloride ●
Methaqualone (blood level above 3 mg/100 ml)
Paracetamol (after massive dosage)
Phenacetin (after massive dosage)
Salicylates:
Aspirin – level above 90 mg/100 ml
Methyl salicylate symptoms in child

● Nephrotoxic exogenous poisons

In spite of this extensive list of dialysable poisons and indications, we dialyse some 6 per 1,000 poisoning admissions. Glutethimide is not a common poison with us, but methaqualone poisoning (in its various preparations) is not uncommon. Of 44 dialyses for poisoning, mostly for barbiturates (16) and aspirin (14), there have been 8 deaths.

There is no doubt that some barbiturates (phenobarbitone, barbitone) are removed by hæmodialysis up to 30 times more quickly than diuresis. Phenobarbitone clearance with the Twin-coil may exceed 50 ml per minute depending upon blood flow, and higher clearance figures are reported using the 4-layer Kiil or the Skeggs-Leonards kidney. In my experience a ten-hour dialysis for phenobarbitone can remove 4 g of the drug, but higher figures have been reported.

Although the short-acting barbiturates, quinalbarbitone, amylobarbitone, pentobarbitone and butobarbitone, are dialysable, it is very difficult to assess accurately what effect the dialysis has on the length of coma; certainly clearance figures *in vivo* are less than for phenobarbitone and barbitone; probably on balance, excluding quinal barbitone, duration of coma is shortened. Blood barbiturate levels in excess of 4·5 mg/100 ml for short-acting or 20–30 mg/100 ml for the longer-

acting have been considered indications for hæmodialysis. Our experience is that survival with very high blood levels of barbiturate is the rule without hæmodialysis. Only clinical deterioration in association with high levels, association of other poisons – very common with barbiturates, or other clinical factors, e.g. anuria, should be the indication for dialysis rather than blood levels alone, unless the blood levels are fantastically high, though even here there are problems of interpretation. Thus there is a case on record where a blood amylobarbitone level was reduced from 16 mg/100 ml with survival of the patient after hæmodialysis (Terplan & Unger 1966). On the other hand I have had a patient with a blood level of 15 mg/100 ml of butobarbitone who made an uneventful recovery without hæmodialysis or peritoneal dialysis. In my own experience blood levels of the quick-acting barbiturates up to as high as 7 mg/100 ml mostly do not present insuperable clinical problems; if the patients are alive when admitted to hospital they survive with very few exceptions and without hæmodialysis.

To sum up the situation regarding the barbiturates, hæmodialysis is only exceptionally necessary, judgment for hæmodialysis must be primarily clinical, blood levels being of some guidance concerning the long-acting drugs, and it is probably of no value where short-acting drugs are concerned. The presumptive quantity of barbiturate ingested is of little significance. In favour of hæmodialysis would be associated ingestion of other drugs and alcohol, deteriorating clinical state, prolonged respiratory failure, circulatory collapse, refractory hypotension, hypothermia, oliguria and anuria. If hæmodialysis is carried out it should be continued for up to 14 hours, unless the patient recovers consciousness, the symptoms dramatically improve or the blood barbiturate level falls precipitously to well below a safe level.

Glutethimide poisoning is far less common in our experience than barbiturate or methaqualone poisoning. The single patient submitted to extracorporeal hæmodialysis died. Of the remaining dozen that I can trace from our more recent records, there has been one death. Both fatal cases had blood levels of 3·5 mg/100 ml. These figures are too small to be significant, but the published case records suggest a mortality rate of about 40% for those not submitted to hæmodialysis, and half that mortality for those dialysed. The well-known facts of body fat sequestration of glutethimide and recycling via liver and biliary excretion and protein binding all tend to diminish the value of hæmodialysis. In hæmodialysis actual drug dialysate recovery has been minimal, and this has favoured the idea of using fat emulsions in the dialysate, which experimentally have increased the clearance two- to three-fold. Prolonged coma, known ingestion of considerable quantities of the drug (more than 10 g), high blood levels (over 3·0 mg/100 ml) would all suggest a trial of extracorporeal hæmodialysis, possibly in association with one or more other methods (peritoneal dialysis).

Extracorporeal hæmodialysis is valueless in poisoning by phenothiazine compounds (chlorpromazine – Largactil), dibenzazepine compounds (imipramine, amitriptyline) and benzodiazepine compounds (chlordiazepoxide – Librium; diazepam – Valium; probably nitrazepam – Mogadon; and probably oxazepam – Serenid-D).

Aspirin is another very common poison. It lends itself to a considerable amount of experimental work and clinical study because of the ease of estimation of the drug in the blood and because of the close relationship between clinical state and blood level, at least in adults during the early hours of the intoxication. Again I would deprecate any clinical assessment based on quantity of drug ingested – we have had recovery of patients after the ingestion of vast quantities of aspirin and without hæmodialysis or forced alkaline diuresis. One man aged 30 walked into the admission unit claiming he had taken 500 tablets of aspirin about an hour previous and had not vomited. He was not believed, but nevertheless was given the treatment. Gastric aspiration produced some 70–80 g in a large volume of turbid almost pultaceous suspension and the equivalent of a further 20 g was obtained from his urine over the next 48 hours, but at no time did his blood level exceed 70 mg/100 ml and he was never unduly distressed. In our experience an adult's death is exceptional at levels under 100 mg/100 ml with any pattern of standard treatment, and unknown below 90 mg/100 ml. Above 100 mg/100 ml recoveries have been reported with hæmodialysis, forced alkaline diuresis and osmotic diuresis, and most therapies claim a survival after a blood level as high as 140 or 150 mg/100 ml – nevertheless most have quite a few deaths also at these levels and lower. The requirements of success here seem to depend upon a slow increase in blood level to the highest figure and easy accessibility of effective treatment. Since some 10% of these patients have also ingested another poison – often alcohol – any therapeutic decision must take this possibility into consideration. We favour hæmodialysis in association with forced alkaline diuresis for all adult patients with blood levels in excess of 100 mg/100 ml – and serious consideration of extracorporeal hæmodialysis where the blood level is 90 mg/100 ml or higher, or the patient has definitely ingested another poison with aspirin and his clinical condition is deteriorating, he has profound biochemical changes or his blood level

is rapidly increasing in spite of therapy. Using a Twin-coil kidney one could expect a clearance figure in excess of 50 ml/min with blood flow exceeding 350 ml/min. One might expect a fall in blood level in excess of 20 mg/100 ml per hour initially (50–60 mg/100 ml in the first three hours) and recovery of aspirin equal to one-third of the ingested dose, as much as 15 g after dialysis, which should be continued until the blood level is below 30 mg/100 ml. The 4-layer Kiil dialyser could be expected to give comparable figures.

Methyl salicylate poisoning will give much the same response as aspirin, with comparable clearance figures.

In children the level of salicylate in the blood is not a good criterion alone as to the prognosis – the clinical state is of paramount importance – stupor, delirium and hyperpyrexia are ominous manifestations, and in these circumstances hæmodialysis must be considered in association with alkaline diuresis and possibly exchange transfusion. Children, including those under 1 year of age, have been successfully dialysed for poisoning (Kallen *et al.* 1966, Fine *et al.* 1968, Spritz *et al.* 1959).

Finally, hæmodialysis is of outstanding value in the treatment of poisoning by ethyl and methyl alcohol, the clearance being between 90 and 150 ml/min. Though only exceptionally indicated in ethyl alcohol intoxication where the blood level falls about ten times faster than normal, it is the method of choice in methyl alcohol where the blood level falls some 50 times faster than spontaneous clearance (Wieth & Jørgensen 1961, Austin *et al.* 1961, Cowen 1964). It is the only treatment worth considering that has any significant effect on the eventual outcome. Similarly it is the treatment of choice in ethylene glycol poisoning where institution of this treatment must not be delayed until the patient is oliguric and dangerously ill.

In conclusion, hæmodialysis, in the context of this paper, must be considered as an adjunct to the treatment of poisoning. It is not a substitute for rational management on sound medical principles. It is needless to say that its use is confined to a relatively minute group of cases. Probably not above 3% of patients admitted for acute poisoning justify the use of the more 'esoteric' therapeutic procedures and hæmodialysis is just one of these.

Much has been written on the great value of this or that therapy in individual cases of poisoning or small groups of patients; nevertheless in the British Isles certain facts stand out. Excluding the gaseous poisons, since 1936 there has been an annual increase in the total number of deaths from poisoning, and for some years the increase has been considerable. Since 1936 there has been at least a hundredfold increase in the number of patients admitted to hospital for the treatment of poisoning, but most deaths from poisoning occur outside hospital (ratio approximately 3:1) so that in some respects the hospital population is artificial and highly selected. The mortality rate for the treatment of poisoning in hospital has fallen considerably in the past 30–35 years, being about 1·5–2·0% overall in the British Isles. For barbiturate poisoning it was about 15% in 1936–39, about 6% for the immediate post-war period (1947–50) and it is not above 1% now. The point I am trying to make here is that although a method of treatment may achieve certain results in an individual case, its overall impact on the 'poisoning scene' may be unimpressive or non-existent. In spite of much that has been said and written the primary object of treatment is not to remove as much poison as possible from the patient by any available means; it is, first, to save the patient's life if it is in danger and, secondly, to relieve him as far as possible of pain and suffering immediate and remote.

REFERENCES

Abel J J, Rowntree L G & Turner B B (1914) *J. Pharmacol. exp. Ther.* **5**, 275
Austin W H, Lape C P & Burnham H N (1961) *New Engl. J. Med.* **265**, 334
Cowen D L (1964) *Ann. intern. Med.* **61**, 134
Doolan P D, Walsh W P, Kyle L H & Wishinsky H (1951) *J. Amer. med. Ass.* **146**, 105
Fine R N, Stiles Q, DePalmer J R & Donnell G N (1968) *Amer. J. Dis. Child.* **116**, 657
Hagstam K E & Lindholm T (1964) *Acta med. scand.* **175**, 507
Jørgensen H E & Wieth J O (1963) *Lancet* i, 81
Kallen R J, Zaltzman S, Coe F L & Metcoff J (1966) *Medicine (Baltimore)* **45**, 1
Schreiner G E (1958) *Arch. intern. Med.* **102**, 896
Schreiner G E & Maher J F (1960) *Bull. New Jersey Acad. Med.* **6**, 310
Spritz N, Fahem J J, Thompson D D & Rubin A L (1959) *Pediatrics* **24**, 540
Terplan M & Unger A M (1966) *J. Amer. med. Ass.* **198**, 322
Wieth J O & Jørgensen H E (1961) *Dan. med. Bull.* **8**, 103

The following papers were also read:

Historical Review of Hæmodialysis.
Dialysis of Acutely Ill Patients with Recoverable Lesions
Dr A M Joekes
(*Institute of Urology, London*)

Chronic Intermittent Dialysis
Dr John Curtis (*Charing Cross Hospital Medical School, Fulham Hospital, London*)